ANNEX

CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT TO BE IMPLEMENTED BY THE MEMBER STATES

CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT TO BE ADDRESSED TO THE MEMBER STATES

The EU Member States shall ensure that:

The MAH shall set up a surveillance programme to collect information on: the demographics of patients prescribed Thelin, any adverse reactions and reasons for discontinuation of Thelin. Details of such a surveillance programme should be agreed with the National Competent Authorities in each member state and put in place prior to marketing of the product.

The MAH must agree the details of a controlled distribution system with the National Competent Authorities and must implement such programme nationally to ensure that, prior to prescribing, all doctors who intend to prescribe Thelin are provided with a physician information pack containing the following:

- Product information
- Physician information about Thelin
- Patient information card
- Partner of patient information card

The physician information about Thelin should contain the following key elements:

- That Thelin is teratogenic
    - Use of effective contraception in women of child bearing age
    - Possible interaction with oral contraceptives and increased risk of thromboembolism
    - Need to advise female patients about teratogenicity, contraception, if necessary the need for pregnancy testing and what to do if they become pregnant
    - Referral of patients who become pregnant to a physician specialised or experienced in teratology and its diagnosis for evaluation and advice

- That Thelin is hepatotoxic
    - Need for liver function tests prior to and during treatment
    - Contraindication in patients with pre-existing hepatic impairment (Child-Pugh Class A-C).
    - Contraindication in patients with elevated direct bilirubin > 2 x ULN prior to initiation of treatment.
    - Need for close monitoring if liver enzymes measure > 3 × upper limit normal (ULN):
        - > 3 and ≤ 5 × ULN: Confirm by another liver test; if confirmed, a decision should be made on an individual basis to continue or to stop Thelin administration. Continue to monitor aminotransferases at least every 2 weeks. If the aminotransferase levels return to pre-treatment values consider resuming the initial treatment schedule.
        - > 5 and ≤ 8 × ULN: Confirm by another liver test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks until levels have normalised. If the aminotransferase levels return to pre-treatment values, reintroducing Thelin may be considered.
        - > 8 x ULN: treatment must be stopped and reintroduction of Thelin is not to be considered.

- That treatment with Thelin often causes a decrease in haemoglobin and related red cell parameters
    - Need for full blood count prior to use and monitoring at clinically appropriate intervals

- Effect of Thelin on bleeding
    - Interaction with warfarin and vitamin K antagonists leading to an increased INR
    - Need to decrease established dose of vitamin K antagonist upon starting sitaxentan therapy
    - Start vitamin K antagonists treatment at a reduced dose if already on sitaxentan sodium
    - Need for regular monitoring of INR
    - Be aware of the potential for haemorrhage and investigate as appropriate

- Increased risk of epistaxis and gingival bleeding

- That there is an interaction with ciclosporin A which may lead to higher blood concentration of Thelin and hence an increased risk of adverse reactions.

- That the safety database of Thelin is limited and physicians are encouraged to enrol patients in a surveillance programme to increase knowledge about the incidence of important adverse drug reactions (ADRs). The surveillance programme should prompt doctors to report serious ADRs and certain selected ADRs as below immediately and other non-serious ADRs at three monthly intervals.

The information collected should include:

- Anonymised patient details – age, sex and aetiology of PAH
- Concomitant medications
- Reason for discontinuation
- ADRs
- All serious ADRs
- Increase in hepatic enzymes to > 3 × ULN
- Elevated direct bilirubin > 2 × ULN
- Anaemia
- Haemorrhage
- Pregnancy and outcome
- Pulmonary oedema (associated with veno-occlusive disease)
- Suspected interactions
- Unexpected ADRs according to the SPC.

The Patient information card should include the following information

- That Thelin is teratogenic
- The need to ensure that women of child bearing age are using effective contraception and that patients should inform their doctors of any possibility of pregnancy before a new prescription is issued
- The need for female patients to contact their treating doctor immediately if they suspect that they might be pregnant.
- That Thelin is hepatotoxic and they will need to attend for regular blood tests
- The need to tell their doctor about any adverse events
- The need to tell their doctor that they are taking Thelin

Partner of patient information card should include the following information:

- That Thelin is teratogenic and that women of child bearing age must use effective contraception